

Challenges to Developing an Effective Vaccine for Newborn Calves

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Project Title:

Recombinant Bovine C3d as an Adjuvant to Facilitate Early Calthood Vaccination

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Background

Calves are born before their immune systems are fully developed. A newborn calf relies on maternal antibodies from the dam's colostrum for disease protection (passive immunity) until the calf's immune system (active immunity) becomes fully functional. The transition between passive and active immunity occurs at approximately 6 weeks of age. If calves could be vaccinated effectively in the first weeks of life, antibodies produced by the calf active immune system would take over to protect the calf as protection from the maternal antibodies in the colostrum decreases.

So far, early calthood vaccination has not been very effective for two reasons. First, the calf's immune system is immature. Second, the active immune cells that the calf does produce are inhibited by maternal antibodies. A better understanding of the neonatal immune system may help develop vaccines that are more effective in newborn calves.

B lymphocytes (B cells) are white blood cells that play an important front-line role in the active immune response. B cells detect and respond to foreign cells like disease organisms. This project studied two receptors on the surface of B cells. These receptors are called CD21 and CD32, and they can have opposite effects on the calf's active immune response. The CD21 receptor binds a protein called C3d, which is also produced by the active immune system. If the C3d is bound to an antigen from a foreign cell, the B cell is alerted that a foreign cell has been detected, and the immune response is massively amplified to attack those foreign cells. C3d is found in high concentrations in adult cattle, but in low levels in newborn calves. As a result, adding C3d to vaccines for young calves may help activate B cells and enhance antibody responses. However, the CD32 receptor binds maternal antibodies. If the maternal antibody is bound to an antigen, the active immune response through the CD21 receptor is inhibited. The expression of CD21 (which activates the active immune response) and CD32 (which inhibits the active immune response) by B cells from neonatal calves needed to be evaluated before vaccine trials were pursued further.

Objectives

To characterize the activating and inhibitory receptors on B lymphocytes and conduct experiments to better understand how complement component C3d might be used to develop effective calthood vaccines. This builds on earlier research funded by the BCRC.

What they did

The researchers examined B cells from calves up to 6 months of age. Two alternative forms of the CD32 receptor were detected which had never been found in cattle before. A highly sensitive technique was developed to distinguish expression of the various forms of CD32 in the B cells of newborn calves. Pilot experiments were carried out to assess the reactivity and effectiveness of C3d as a vaccine component.

What they learned

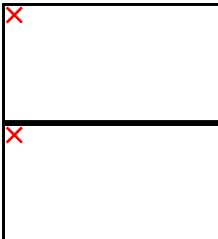
Even at birth, 90% or more of blood B cells expressed both CD21 (activating) and CD32 (inhibitory) receptors. However, the number of B cells in blood was less than 20% of that in adults, and the intensity of CD21 and CD32 receptor expression was lower in calves than in adults. The CD32 receptors reached adult levels in only three weeks, while the CD21 receptors reached adult levels at 6 weeks of age. The greater inhibitory action of CD32 receptors versus the activating action of CD21 receptors at 3 weeks of age is likely part of the challenge in developing an effective vaccine for newborn calves. To make things even more complicated, the two distinct forms of the CD32 receptor discovered in this study also appear to inhibit active immune responses by two different mechanisms in newborn calves.

Vaccines with different formulations of C3d and containing a model antigen were developed and administered to 14-day and 6-month-old calves to assess local reactions at the injection sites and their abilities to increase antibody responses. No symptoms of toxicity were observed. However, adding C3d did not strengthen the immune response, either. More work is underway to develop alternative strategies to improve C3d formulation and improve the effectiveness of the experimental vaccine.

What it means

This research was conducted to learn more about the complex changes the immune system undergoes during the transition between passive and active immunity in young calves. This research has not yet developed an improved vaccine. However, this new knowledge about the immune system's activating and inhibitory signals will help in future efforts to develop more effective vaccines for use in newborn calves.

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